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Review Paper

A Comparision of US, Europe, Japan and India Biosimilar Regulations

Rajput Bane Singh*
Lachoo Memorial College of Science & Technology, Pharmacy Wing, Jodhpur (Raj.), India

Abstract

A biosimilar is a biological medicine that is similar, but not identical, to an already registered reference biotherapeutic product in terms of quality, safety, and efficacy. These drugs may be also called as biosimilar products', follow-on protein products' and subsequent-entry biologics'.

The United States enacted the Biologics Price Competition and Innovation Act (BPCI) in the end of March 2010 to providing an application pathway for follow-on biological products under sections 7001 to 7003 of the Patient Protection and Affordable Care Act and also codified in 42 USC 262(k).

In Europe, in 2001, legislation concerning biosimilar was codified as Directive 2001/83/EC to create a new marketing authorization procedure for similar biological medicinal products and also Committee for Medicinal Products for Human Use (CHMP) of the EMA is concern with these biosimilar products.

The Ministry for Health Labour and Welfare (MHLW) is the regulatory body in Japan responsible for the scientific evaluation and approval of biosimilar medicines developed by pharmaceutical companies for use in Japan and in March 2009, biosimilar guidelines published by the MHLW.

In India, Review Committee on Genetic Manipulation (RCGM) and Genetic Engineering Approval Committee (GEAC) of Central Drugs Standard Control Organization (CDSCO) is responsible for the development and preclinical evaluation of recombinant biologics drugs.

This article having precise, concise, and simple comparison of US, Europe, Japan, and India related to biosimilar drugs regulations and litigation.

*Corresponding author, Mailing address:
Bane Singh Rajput
Research Scholar in Pharmaceutical Management and Regulatory Affairs of Lachoo Memorial College of Science & Technology, Pharmacy Wing, Jodhpur (Raj.) India. Postal Code-342001
Email-bnsingh29@gmail.com

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INTRODUCTION

Biosimilars are biologic medical products whose active drug substance are made by a living organism or derived from a living organism by recombinant DNA or controlled gene expression methods. A biosimilar is a biological medicine that is similar, but not identical, to an already registered reference biotherapeutic product in terms of quality, safety, and efficacy and intended to have the same

mechanism of action for the same diseases as the innovator biopharmaceutical drugs.These drugs may be also called as biosimilar products', follow-on protein products' and subsequent-entry biologics. Biosimilars are generally exhibit high molecular complexity and may be quite sensitive to changes in manufacturing processes, starting material and method of control.[1]

The global biosimilars market is expected to be worth $19.4 billion by 2014, growing at a Compound Annual Growth Rate (CAGR) of 89.1% from 2009 to 2014.[2]

Biological products worth $25 billion are going to be off patent by 2016 and this will open a pathway for the drug manufacturers to increase their market share, profit margins and reduce the medical expenditure of biosimilar products.[3]

Regulatory Framework in United States

On 23 March 2010, the US President signed into law a bill governing the regulation of biosimilars. The Biologics Price Competition and Innovation Act of 2009 (BPCIA) permits the licensing of biological products that are shown to be biosimilar to previously licensed reference products. BPCI provides an application pathway for follow-on biological products, codified in 42 USC 262(k). [4]

For this purpose, the FDA has established three committees to ensure consistency in the FDA's regulatory approach of follow-on biologics. The three committees are the Center for Biologics Evaluation and Research (CBER), Biosimilar Implementation Committee (BIC), and the CBER Biosimilar Review Committee. The CBER BRC will focus on the crosscenter policy issues related to the implementation of the BPCI Act.[5]

On February 9, 2012, FDA announced the publication of three draft guidance documents to assist industry in developing follow-on biologic products, including "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product", "Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product", and "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009".[6]

Regulatory Framework in Europe

The European Union (EU) has pioneered in the development of a regulatory system for biosimilar products.

In January 2001, The European Medicines Agency (EMA) began formal consideration of scientific issues presented by biosimilar products.[7]

In 2003, the European Commission amended the provisions of the EU secondary legislation governing requirements for marketing authorization applications for medicinal products and established a new category of applications for "similar biological medicinal products".

In 2005, the EMA issued a general guideline on similar biological medicinal products.

In 2011, a concept paper on the revision of the guideline on similar biological medicinal products was published by EMA.[8]

In order to grant a biosimilar product, the EMA requires that the active substance, the pharmaceutical form, strength, route of administration of the biosimilar should be the same as reference product and comprehensive and justified comparability studies between the biosimilar and the reference products in the quality, nonclinical, and clinical level, which are explained in detail in the EMA guidelines.[9]

Regulatory Framework in Japan

Japanese Ministry of Health, Labor and Welfare (MHLW) has also been confronted with the new challenge of regulating biosimilar or follow-on biologic products. Based on the similarity concept outlined by the EMA, Japan has published a guideline for quality, safety and efficacy of biosimilar products in 2009.

The scope of the guideline includes recombinant plasma proteins, recombinant vaccines, PEGylated recombinant proteins, and non-recombinant proteins that are highly purified and characterized. Unlike in the EU, polyglycans such as low-molecular weight heparin have been excluded from the guideline. Another class of products excluded is synthetic peptides, According to this guideline, two follow-on biologics, "Somatropin" and "Epoetin alfa BS" have been recently approved in Japan.[10]

Table 1: Comparation Parameters of US, Europe, Japan, and India

Parameters	US	Europe	Japan	India
Term	follow-on biologics (FOBs)	Biosimilars	Follow-on Biologics	similar biologics products or Biogeneric
Definition	A product highly similar to the reference product without clinically meaningful differences in safety, purity and potency	Biological products which demonstrated its equivalence to an already approved reference product with regard to quality, safety, and efficacy	A biosimilar prodct is a biotechnological drug product developed by a different company to be comparable to an approved biotechnology-derived innovator product	Biosimilars are defined as officially approved new version of innovator biotherapeutic products for which the patent has expired
Laws and Regulation	Biologics Price Competition and Innovation Act (BPCI)	Committee for Medicinal Products for Human Use (CHMP) of the EMA	Ministry for Health Labor and Welfare (MHLW)	Review Committee on Genetic Manipulation (RCGM) and Genetic Engineering Approval Committee (GEAC) of Central Drugs Standard Control Organization (CDSCO)
Reference Product	Authorized in US	Authorized in EU	Authorized in Japan	Authorized in India
data exclusivity	12 Years, A section (k) application may not be filed until 4 years after reference product approval	11 Years, comprising 10 years for new biologics (8-year data exclusivity and 2-year market exclusivity) and a 1-year extension For a new indication.	Not Specified	Not Specified
Pre-litigation procedure	Present	Absent	Absent	Absent
Jurisdiction	Pre-clinical and clinical investigation is exempt from infringement under 35 U.S.C. 271(e) (1).	Conducting necessary trials or studies for biosimilar approval is not infringement under Article 10(6) of Directive 2004/27/EC.	Not Defined	Not Defined
Interchangeability	Present	Absent	Absent	Absent
Data Requirement	Analytic data that show similar to the reference , animal studies, Clinical studies, identity of mechanism of action	Purity, Physiochemical properties, Biological activity, Clinical studies, Preclinical, and Immunogenicity studies	Clinical studies, Preclinical, and Immunogenicity studies	Biological activity, Clinical studies, Preclinical, and Immunogenicity studies
Guidance	Published guidance under 262(k) (8).	Published guidance under CHMP/437/04., EMEA/CHMP/BWP/49348/2005., and EMEA/CHMP/BMWP/4035	Published guidance under MHLW	Published guidance under CDSCO.
Stability Requirement	Long Term and Accelerated	Accelerated and under stress condition	Not Necessary	Long Term and Accelerated

Regulatory Framework in India

In India, Central Drugs Standard Control Organization (CDSCO) is the apex regulatory body under Government of India (GoI) related to biosimilar.

Two other competent authorities are involved in the approval process of biosimilars or Similar Biologics products (SBPs).

i. Review Committee on Genetic Manipulation (RCGM), which works under Department of Biotechnology (DBT), Ministry of Science and Technology.

RCGM regulates import, export, carrying out research, preclinical permission, No objection certificate for clinical trial (CT) and other related activities involving genetically modified organism (GMO), as per the DBT guidelines.

ii. Genetic Engineering Approval Committee (GEAC), which functions under the Department of Environment (DoE)

GEAC as a statutory body for review and approval of activities involving large scale use of genetically engineered organisms and their products in research and development, industrial production, environmental release and field applications.

CDSCO proposed guideline addresses the requirements regarding manufacturing process, quality aspects, and pre-market regulatory requirements including comparability exercise for quality, non-clinical and clinical studies and post market regulatory requirements for biosimilar.

Table 2: Laws and Regulatations Related to Biosimilar of US, Europe, Japan and India

S. No	Countries	Laws and Regulations
1	US	Biologics Price Competition and Innovation Act (BPCI)
2	Europe	Committee for Medicinal Products for Human Use (CHMP) of the EMA
3	Japan	Ministry for Health Labor and Welfare (MHLW)
4	India	Review Committee on Genetic Manipulation (RCGM) and Genetic Engineering Approval Committee (GEAC) of Central Drugs Standard Control Organization (CDSCO)

Table 3: Biosimilar drugs in the US market

S. No.	Trade Name	Descriptive Name	Company
1	GlucaGen	Glucagon, rDNA	Novo Nordisk
2	Omnitrope	Somatropin, rDNA	Sandoz/Novartis

Table 4: Biosimilar drugs in EU market

S. No	Reference product name	Biosimilar product Name	INN name	Company
1	Genotropin	Omnitrope	Somatropin (human growth hormone)	Sandoz Intn'l Ltd.
2	Eprex	Silapo	Epoetin zeta	Stada Arzneimittel AG
3	Eprex	Retacrit		Hospira Inc.

Table 5: Biosimilar drugs in Japan

S. No.	Name
1	Somatropin BS
2	Epoetin alpha BS

Table 6: Biosimilar drugs manufactured and marketing in India

S. No.	Name	Company
1	Chorionic gonadotropin	Reliance Life Sciences
2	Darbepoietin	Dr Reddy's Labs
3	PEG - Interferon alfa	Intas Biopharmaceuticals Virchow Biotech Pvt. Ltd
4	Rituximab	Dr Reddy's Labs
5	Tissue Plasminogen Activator (tPA) - Reteplase	Reliance Life Sciences

CONCLUSION

Europe has been way ahead of the other countries including US in terms of developing biosimilars. Regulatory requirements for the approval of biosimilar products are similar but slightly different in the definitions of biosimilarity, the scope of the guidelines, the choice of the reference product, and the data required for product approval and some other aspects. The Indian government has taken several initiatives towards streamlining the way biosimilars/SBP will be regulated in our country. These steps would ensure more affordable biosimilar

drugs being manufactured and made available to patients both in domestic and export markets

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